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Primary central nervous system lymphoma

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Contents

Abstract

Primary central nervous system lymphomas (PCNSL) are aggressive malignancies that arise in distinct anatomical sites, which display unique structural, biological and immunological conditions. So far, despite recent therapeutic advances, these malignancies exhibit one of the worst prognoses among all non-Hodgkin lymphomas (NHL). For a long time, radiotherapy (RT) has been the standard treatment, producing a response rate of 60–65% and a notable neurological improvement in most cases. However, relapse usually occurred within a few months after RT, with a median survival of 14 months and a 5-year survival of approximately 15–24%. Although the introduction of systemic chemotherapy has consistently improved survival, the prognosis of PCNSL is still dismal, with high rates of local relapse and consequent death. Defining the optimum therapeutic management is difficult because of potential selection biases in large retrospective reviews and the limited number of prospective studies. Although studies published on PCNSL are increasing, several therapeutic questions still remain unanswered after a decade of research.

Keywords: PCNSL; Radiotherapy; Cerebrospinal fluid; Methotrexate; Temozolomide; Rituximab

1. Incidence and risk factors

PCNSL, once called microgliomas reticular cell sarcomas or perivascular sarcomas [1] are rare tumours. They comprise

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0.5–1.2% of intracranial neoplasms and less than 1% of extranodal non-Hodgkin's lymphomas (NHL) [2]. A progressive increase in the incidence of PCNSL has been observed in the last decade, both in individuals affected by immunodeficiencies [2,3] and in the general population [4]. Its incidence increased nearly three-fold between 1973 and 1984 [5], but, recent data suggest that it may be stabilizing or declining slightly [6]. An epidemiological study has shown that the incidence of PCNSL has tripled in the apparently healthy population. The reasons are unknown, and cannot be attributed solely to progress in diagnostic expertise [5]. Should this trend continue at its current rate, in the next decades PCNSL will probably become the most frequent brain neoplasm [2,7].

In spite of having very similar radiologic and histopathologic characteristics, PCNSLs in immunocompetent patients differ substantially from a clinico-epidemiological and prognostic point of view from PCNSLs which develop in immunodeficient patients [8]. The relationship of PCNSL with immunodepression of viral [9], iatrogenic [2] or congenital [10] origin is well known. While Epstein–Barr virus and c-myc proto-oncogene translocation induce the proliferation of PCNSL in HIV patients by a known mechanism, PCNSL in apparently immunocompetent patients, who constitute the majority of cases, arises in an unknown way. By contrast to other lymphomas, there is not sufficient evidence to propose a hereditary component in the pathogenesis of PCNSL. However, O'Neill et al. [11] reported a 30-fold increase in risk for the development of a PCNSL in families with a history of malignancies. Several authors have also reported the appearance of a PCNSL as a second neoplasm [12]. This phenomenon could be linked to a genetic predisposition or to the carcinogenic effect of the antineoplastic therapy administered for treating the first tumour. PCNSL are mostly present in individuals over 60 years old, which is probably related to a reduction of immunological vigilance, particularly of T-lymphocytes. The proliferation of B-lymphocytes produced by chromosomal abnormalities or by viral stimulation might give rise to the development of a monoclonal lymphoma due to the lack of suppressive activity of T-cells. This proliferation is particularly facilitated in the extranodal areas which have unique immunological characteristics, such as the central nervous system. It is well documented that lymphocytic migration inside the nervous tissue depends on a selective interaction of the lymphocytic molecules of adhesion with the vascular endothelium of the CNS. These interactions would at least partially explain the relationship of the neoplastic lymphocytes with the vessels and their successive localization in the perivascular spaces determining the characteristic vasocentric proliferation of the PCNSL. Additionally, a hypothetical "homing receptor" system of the cells of PCNSL could explain their tendency to remain within the CNS and the low incidence of systemic spread of these neoplasms. Several diseases are associated with immunological impairment which has been widely described as a predisposing factor to lymphoproliferative malignancies. It is possible that some epithelial and lymphoreticular tumours or their treatment could induce the immunological suppression responsible for the occurrence of second malignancies, or that general disturbances of immunity predispose to the development of multiple neoplasms. Alternatively, the presence of distinct tumours in the same patient might simply be a coincidence or a consequence of prolonged survival time in cancer patients.

2. Pathology and biology

The histological confirmation of PCNSL diagnosis is extremely important, but it often presents some difficulties due to the site of involvement and the patient's poor performance status. However, modern immunohistochemical and molecular techniques make a diagnosis possible with a minimum of tissue sampled by stereotactic biopsy. No immunophenotypical or genotypical differences have been observed between PCNSL and all other NHLs. Most PCNSL have B-immunophenotype [2,8] that can be confirmed by immunoglobulin light or heavy chains gene rearrangement (most frequently 1 g M/k). Unlike PCNSL in the presence of immunodeficiency, in the immunocompetent individuals these neoplasms show monoclonal proliferation in 90% of cases [2,13]. T-cell PCNSL are rare (1–2%), even though an increase in incidence among immunocompetent patients has been observed [14] mostly in meningeal localisations [15]: their clinical characteristics seem identical to B-cell PCNSL and would need the same therapeutic approach. In contrast to immunodeficient patients [16], few immunocompetent patients are affected by PCNSL in which the Epstein–Barr virus genome is present in the neoplastic cells. In 60–90% of cases, PCNSL are predominantly diffuse large-cell, immunoblastic, lymphoblastic or Burkitt's lymphomas. Only 20–30% of immunocompetent patients are affected by aggressive lymphomas. The follicular pattern of growth is rare: the most significant published series [3] reported a 14% incidence of indolent lymphomas, while other authors observed low-grade PCNSL in 3–50% of cases [2,7]. In 80% of cases, histological appearance consists of vasocentric proliferation with infiltration of the cerebral parenchyma among the involved vessels. The histological margins are cloudy and lymphomatous cells can be found at a distance from the macroscopic margins of the lesion. An extended necrosis can be observed occasionally [11]. Frequently, a certain degree of infiltration of macrophages and an intense astrocytic reaction can be observed. Several models of cellular differentiation have been described, e.g. plasmacytic or plasmacytoid [1]. A histological characteristic of PCNSL is the multiplication of the basal membranes of the blood vessels encased by the neoplasm [1]. When stained with silver salts, these structures are highlighted like a network that has given rise to the name "reticular sarcoma". Even though retrospective studies with sufficient numbers of cases are not available, it seems that the histotype has no prognostic value and therefore would not influence therapeutic choice or treatment response

[3,17]. Some extremely rare histological forms of PCNSL such as solitary intracranial plasmacytoma and intravascular lymphoma [18] have been described. Only 15 cases of the former have been reported, all of them with a prevalently meningeal localization. The latter is a fatal neoplasm characterized by the intravascular multifocal proliferation of large cells that can strike any vessel, including those of the CNS.

The alterations of cerebrospinal fluid (CSF), even though they are not specific and are variable, are very useful for diagnosis orientation. In 65% of the cases protein concentration is increased [1,19], while glucose concentration is generally normal, being reduced only in the case of diffuse meningeal infiltration. CSF cytology examination is very important to allow diagnosis of PCNSL in patients that cannot be biopsied due to their poor clinical condition. Moreover, it seems to have a fundamental value in staging, which has potential prognostic and therapeutic implications. Unfortunately, it is not possible to identify lymphomatous cells in every case and sometimes not even in the presence of an extended meningeal infiltration. By contrast to the situation in systemic lymphomas involving the CNS, in which the cytological examination of the CSF is positive in 70–95% of the cases, the most significant series on PCNSL showed a positivity of CSF in 0–50% of the patients (median: 16%) [20]. Modern immunohistochemical methods, and techniques of molecular biology should soon extend the diagnostic potential of this technique. When the neoplastic cells cannot be detected by classical histological techniques, the study of lymphocytic pleiocytosis that is noticed in the CSF in half of the patients assumes an important role. Methods of molecular biology could be useful to differentiate tumour cells from non-malignant reactive cells. As described in the paragraph dedicated to histopathology, PCNSL displays two fundamental characteristics that assume a great importance in this situation; their monoclonal proliferation and their prevalently B-immunophenotype. These neoplasms are associated with a polyclonal proliferation of reactive T-lymphocytes in more than half of the cases [10]. Therefore, both the study of clonogenicity and immunophenotype allows the reactive or neoplastic character of the lymphocytic pleiocytosis to be defined [21]. Finally, in some cases, the use of electron microscopy could facilitate the definitive diagnosis [22].

The cells of PCNSL have a variable immunophenotype according to their histological subtype (see the respective lymphoma subtype). One to four percent of PCNSL displays T-cell phenotype [23], which arises to 8% in Japan. The diagnosis of T-cell PCNSL can be difficult and it possibly is overestimated due to the presence of reactive perivascular T-cell infiltrate, which could interfere with the interpretation of immunophenotyping, mostly during steroid assumption. In comparison to B-cell PCNSL, T-cell PCNSL are more commonly associated with male gender and systemic symptoms [24], while leptomeningeal involvement is comparable in B- and T-PCNSL (42% versus 38%). A recently reported large retrospective series of the International PCNSL Collaborative Group [24] concluded that T-cell PCNSL should be treated following the same principles used for the rest of PCNSL, obtaining similar results, at least in Western countries.

A germinal center B-cell-like origin of PCNSL was hypothesized on the basis of BCL-6 expression and ongoing mutational activity. With immunohistochemically techniques, CD10, BCL-6, MUM1, BCL-2, and CD138 immunoreactivity has been reported in 2.4, 55.5, 92.6, 55.5, and 0% of cases, respectively [25]. Ninety-six percent of PCNSL have been be classified as with activated B-cell-like phenotype; 51% express BCL-6 + MUM1+, suggesting an "activated germinal center B-cell-like" origin; 40% are exclusively MUM1 + , and the remaining 5% have been negative for all above-mentioned markers. The activated B-cell-like pattern of PCNSL may, in part, explain the poor prognostic of these malignancies. A histogenetic "time-slot" overlapping late germinal centre and early post-germinal centre has been postulated for PCNSL, which could explain its predominant activated B-cell-like phenotype [25].

3. Diagnosis

3.1. Clinical presentation

PCNSL occur in all age groups. The peak of incidence is between 60 and 70 years of age for immunocompetent individuals [8,26]. The male:female ratio is 1.5:1 [8]. PCNSL are by definition limited to the CNS and therefore considered a stage IE-disease. Systemic symptoms are rarely associated (2% of cases). At the onset, clinical presentation is non-specific and consistent with that of an intracranial mass, with signs of both motor and sensory focal deficits in about 50% of cases. Since these neoplasms show a predilection for localization in the frontal lobe, personality changes are frequent. Often headaches (56%) and other signs of intracranial hypertension such as nausea (35%), vomiting (11%) and papilloedema (32%) are present [7]. Less frequently there are generalized seizures, signs of impairment of the brain stem and the cerebellum and extrapyramidal syndromes. The symptoms resulting from the involvement of the eye precede cerebral symptoms by months or years [27]. At least 80% of the patients with primitive lymphoma of the eye will develop a cerebral lymphoma sometimes after a prolonged latency. Also if clinically silent, its onset is similar to a non-specific monolateral uveitis refractory to conventional ophthalmologic treatment, and associated with floaters or campimeter deficit. While common uveitis shows a hightened sensitivity to topical or systemic corticosteroids, uveitis from lymphoma rapidly becomes resistant to this treatment. Therefore, a persistent uveitis that becomes resistant to corticotherapy should suggest an intraocular localization from PCNSL.

The rapid growth of PCNSL produces a progressive worsening of the neurological performance status: an average of 2–3 months usually elapses between the clinical onset and the radiological diagnosis. PCNSL can arise in the cerebral, cerebellar and the brain stem parenchyma, in the eye,

the leptomeninges and the spinal cord. In more than half of immunocompetent patients, PCNSL present with a single lesion, deeply localized, usually in the periventricular regions infiltrating the corpus callosum and the basal ganglia. Sometimes the neoplasm symmetrically infiltrates both the cerebral hemispheres, giving origin to the typical radiographic "butterfly" image. Only 10–15% of the lesions are localized in subtentorial fossa. PCNSL tend to infiltrate the subependimal tissues, coming into close contact with the ventricular system and disseminating through the cerebrospinal fluid to the meninges [28]. A study based on autopsy findings demonstrated a meningeal involvement in 100% of cases [19]. However, in the most numerous series CSF examination demonstrated lymphomatous cells in less than half of the cases examined. It is probable that the development of new diagnostic techniques of molecular biology will reveal an increased percentage of positive exams. In 5–20% of cases, more often in the multifocal forms, PCNSL begins in an intraocular location. Since the eye is an extension of the CNS, its involvement is not considered a systemic dissemination, even when it is bilateral. In fact, the involvement of both eyes occurs in almost 80% of cases. The neoplastic cells can infiltrate the vitreous humor, the retina, the choroides and less frequently, the optic nerve. A leptomeningeal localization in the absence of a parenchymal mass occurs in less than 10% of cases [2]. The initial symptoms are similar to those of neuropathies or lumbosacral radiculopathies with radicular pain, increase of intrarachidian pressure or confusion. Rarely PCNSL affect the spinal cord [8]. This localisation presents the greatest diagnostic difficulties. The patient generally complains of pain in the limbs, most of all in the legs, and radicular symptoms associated with sensory damage. In these cases the prognosis is very poor with a median survival of few months, mainly due to a late diagnosis. Even though extremely rare, some cases have been described occurring at the level of the cauda equina and the sciatic nerve. Some authors have described a form of PCNSL that infiltrates the spinal nerves and their ganglia. It has been termed neurolymphomatosis, to distinguish it from the infiltration of the nerves by a systemic lymphoma.

3.2. Neuroimaging

In spite of the fact that pathognomonic radiological patterns of PCNSL do not exist, computerized tomography scans (CT) and magnetic resonance (MR) images suggest that it is appropriate to be suspicious of a lymphomatous nature of a cerebral mass. In 90% of cases, the pre-contrast CT scan shows an iso- or hypo-dense, single or multiple, lesion. The lesions, which in general are poorly delimited with scarce perilesional oedema, tend to localize in the deep regions of the brain [8]. The use of contrast media produces an intense and homogeneous enhancement of the image. Only in 12% of patients with PCNSL enhancement is not observed [26]. Enhancement might predict, as well as diagnostic information, response to chemotherapy since this depends on the grade of integrity of the blood–brain barrier (BBB). A lesion with scarce enhancement is generally associated with an intact BBB that could hamper the antineoplastic drug reaching the lymphomatous cells. Enhancement is also observed with MR, while the pre-Gadolinium T1 MR image shows an isointense lesion. The use of MR allows the identification of some lesions, in particular those in the spinal cord, that are not visible by CT scan. The radiographic aspect of brain lesions is common to all PCNSL histotypes and it is useful in the differential diagnosis with demyelination diseases, gliomas, meningiomas, metastasis, sarcoidosis and toxoplasmosis [2,8]. In some cases, periventricular lesions that involve the median deep structures of the brain can present with a "butterfly" image that suggests a malignant glioma. The calcifications that are frequently observed in oligodendrogliomas and low-grade astrocytomas are usually absent in PCNSL. Additionally, most gliomas, both high- and low-grade, in contrast to PCNSL, are generally hypo-dense. In the case of a multifocal presentation or of patients with a prior or concomitant history of malignancy the differential diagnosis between PCNSL and metastasis can be especially difficult [29]. Although cerebral metastasis can be hyper- or iso-dense, they are commonly located at the corticomedullar junction area rather than in the periventricular regions. Moreover, a dramatic response to corticosteroids should raise the suspicion of PCNSL, while the natural history of prior or concomitant neoplasm as well as the location could suggest metastatic disease. In some cases, a diffuse infiltration of the white matter accompanied by a slight enhancement can be observed. This pattern should be distinguished from that of multiple sclerosis and of other leucoencephalopathies. This differential diagnosis is very difficult, not only because the radiographic images are similar, but also because both show a dramatic response to steroids administration. PCNSL can also present on a CT scan like a diffuse and hyper-dense meningeal infiltration which is rare and difficult to distinguish from other meningeal lesions. In spite of the efforts of several authors to find a direct relationship between the radiological and histopathological diagnosis, none of the radiological patterns described corresponds to a particular histotype. Proton magnetic resonance spectroscopy imaging seems to be a useful tool in diagnostic suspicion, response assessment, and early detection of relapse [30]. FDG-PET displays a high sensitivity in PCNSL diagnosis and it may be suitable for therapeutic monitoring [31]. Angiography has a complementary role and is rarely used in PCNSL diagnosis. It allows to distinguish an avascular tumour in 70% of cases [7]. PCNSL lesions do not have a prominent neovascularization and discrepancies between the intense enhancement of the CT and the absence of vascular neoformation in the angiogram have been explained by using positron-emission tomography. Contrary to what happens in gliomas, PCNSL have an intense proliferation of small calibre vessels that allows an abundant tissue perfusion, but which cannot be revealed by angiography. In a third of the cases a diffuse and homogeneous colouration or "blush" that persists from the capillary phase

to the venous phase can be observed, having an appearance similar to that of meningioma [8].

4. Staging

Since PCNSL tend to remain localized in the CNS, some reviews have challenged the actual usefulness of an extensive systemic evaluation in the staging work-up of PCNSL. This conclusion is supported by the fact that, in the large PCNSL series, no case of systemic lymphoma has been found which presented solely with a symptomatic cerebral mass lesion [2,7,26]. In contrast, several authors reported cases of systemic lymphoma which only became evident after complete staging work-up in patients who were initially diagnosed as affected by PCNSL [32–36]. The International PCNSL Collaborative Group (IPCG) has published standardized guidelines for baseline evaluation and staging in PCNSL patients [37]. The extent of disease evaluation should include physical examination, blood count and biochemical profile, a contrast-enhanced brain magnetic resonance imaging (MRI) study, cytological evaluation and flow cytometry of CSF, if a lumbar puncture can be safely performed, a complete ophthalmology evaluation, contrast-enhanced CT scans of the chest, abdomen, and pelvis, and a bone marrow biopsy with aspirate [36]. Testicular ultrasound examination should also be considered in elderly patients [32], while the role of positron-emission tomography in patients with presumed PCNSL remains to be defined. The application of molecular diagnostic techniques may increase these percentages. PCR analysis of IgV_H genes detected identical DNA sequences in bone marrow, peripheral blood and tumour samples in 2 of 24 assessed patients [38]. In one of them, a monoclonal blood product was detectable after 24 months of follow-up despite the complete radiographic remission of the lymphoma [38]. The clinical relevance, if any, of these observations remains to be elucidated. The standard staging system used for PCNSL is the same as that proposed for Hodgkin's disease at the Ann Arbor Conference in 1971 [39].

5. Prognosis

5.1. Natural history

PCNSL are characterized by a rapid growth that is almost always limited to the CNS. As described above, these extranodal lymphomas are considered as stage IE-disease, but their biological behaviour and prognosis are completely different from other lymphomas at the same stage. While other stage-I lymphomas have a 10-year survival rate of 70% of more, the prognosis of PCNSL is ominous, with a 5-year survival rate of 4–40% [20]. The clinical evolution is rapidly fatal if correct treatment is not started immediately and the median survival with only supportive therapy is less than 3 months. Surgery has not improved survival, giving survival rates of 3.5–5 months [20], while it has produced in many cases a clear worsening of the quality of life. Treatment with radiotherapy and corticosteroids has been the standard therapy for several years, with a high complete radiological remission, a significant improvement in neurological performance status and quality of life, and a median survival of 12–18 months [1,40,40]. However, in spite of the elevated percentage of initial complete responses, almost all patients relapse in just a few months from the end of treatment. Moreover, half of the 5-year survivors experience a relapse between 5 and 13 years from diagnosis [11]. In 93% of cases the relapse is local, even within the radiation field [26], while meningeal, spinal and intraocular relapses are less frequent [41,42]. Different from most other extranodal lymphomas, PCNSL show systemic dissemination in only 7–8% of cases. In general, spread consists of a single and asymptomatic lesion, which can be diagnosed only at autopsy [1]. The addition of chemotherapy to radiation therapy has improved survival. In spite of this improvement, the prognosis of PCNSL remains ominous with a great number of local relapses that, after a brief course inevitably lead to death. Treatment of relapses sometimes achieves a complete remission with a lengthening of survival and an improvement in the patient's quality of life [43]. Although results from prospective trials suggest progress in the treatment of PCNSL, survival improvements are not reflected in studies on population-based cohort, and overall survival has not improved consistently in the past three decades [44].

5.2. Prognostic factors

The identification of clinically relevant prognostic factors constitutes an important step forward in the fight against PCNSL. Conversely to those observed for the International Prognostic Index, which is not useful to discriminate among risk groups in PCNSL series [45], the combination of five independent predictors of response and survival, i.e. age, performance status, serum lactate dehydrogenase level, cerebrospinal fluid protein concentration, and the involvement of deep structures of the brain, has allowed to develop a prognostic scoring system that distinguishes three different risk groups based on the presence of 0–1, 2–3 or 4–5 unfavourable features [23,46]. A diffused use of this Prognostic Index, named International Extranodal Lymphoma Study Group (I.E.L.S.G.) score, will allow the separation of patients into risk groups, which could result in the application of risk-adjusted therapeutic strategies, and the comparison of therapeutic results from prospective studies.

6. Treatment

6.1. First-line treatment

The standard treatment for PCNSL has not yet been defined due to the lack of adequate randomized trials.

Retrospective series have inconsistently shown a survival advantage for combinations of chemotherapy and radiotherapy over radiotherapy alone, but this difference could actually be due to selection bias considering the strong prognostic impact of some variables such as age and PS [34]. Therefore, primary chemotherapy containing high-dose methotrexate followed by radiation therapy is suitable for individual clinical use on a type 3 level of evidence [47]. In the vast majority of prospective trials, general criteria for treatment of aggressive NHL were adopted, choosing primary chemotherapy followed by radiation therapy. This strategy produced a 5-year survival of 25–40% [47,48] in comparison to the 3–24% reported with RT alone [34,40]. There are no prospective trials providing therapeutic results obtained with chemotherapy followed by RT versus the inverse sequence (radiotherapy–chemotherapy). However, experimental and clinical [20,45] data support the use of chemotherapy–radiotherapy as the optimal sequence. It is noteworthy that treatment sequence is strongly influenced by the choice of drugs used. Considering that the use of high-dose methotrexate (the main drug in PCNSL management) after radiotherapy has been associated with a high incidence of severe neurotoxicity [45], chemotherapy–radiotherapy should be considered as the only acceptable sequence for high-dose methotrexate delivery. High-dose methotrexate as monochemotherapy followed by radiotherapy is associated with a response rate of 80–90%, a 2-year survival of 60–70% and a 5-year survival of 25–35% [48–50]. Several authors have tried to improve survival by adding other drugs to methotrexate. However, to date, the addition of other drugs at conventional doses did not consistently improve outcome when compared with high-dose methotrexate monochemotherapy [51–53] and has produced a remarkably higher morbidity and mortality [51]. In combined treatment, radiotherapy doses should be decided on the basis of response to primary chemotherapy, and, until definitive conclusions from well-designed trials are available, radiotherapy parameters should follow the widely accepted principles used for other aggressive NHLs [54]. Then, WBRT with 30–36 Gy followed by a tumour-bed boost of 10–15 Gy may be advisable in cases with residual disease, while WBRT with 30 Gy which may or may not be followed by a tumour-bed boost to reach 36 Gy appears suitable for patients in complete remission after chemotherapy. Meningeal involvement has been demonstrated by a positive CSF cytology examination in up to 50% of cases at diagnosis [55]; in more than 20% of cases at relapse [48,50,53], and in 100% of cases at autopsy [19]. These findings seem to support the necessity for meningeal treatment, which can be achieved by spinal-cord irradiation, high-dose systemic chemotherapy or by intrathecal drug delivery. The first strategy is associated with relevant marrow toxicity [8,20], while the indications for and efficacy of different doses of systemic methotrexate and intrathecal chemotherapy are unclear. There are three major aspects limiting the widely use of intrathecal chemotherapy: the lack of a prospective assessment of its survival effect, the increased risk of severe neurotoxicity, especially in patients treated with high-dose methotrexate and WBRT [48,56]; and the impossibility of performing a lumbar puncture or using an Ommaya's reservoir in up to one-third of patients due to elevated intracranial pressure [8]. Some authors assert that meningeal recurrence only occurs in patients with positive CSF cytology at diagnosis, and that intrathecal chemotherapy should be reserved to these patients [48,57]. This is also supported by some prospective trials that evaluated protocols using a methotrexate dose $> 3\ g/m^2$ without intrathecal chemotherapy. Even though these trials reported response and survival data similar to those obtained in series entirely treated with intrathecal drug delivery [48,50], the vast majority of meningeal relapses were actually observed in CSF-positive patients.

There is no standard treatment approach to isolated IOL. Systemic administration of MTX and cytarabine can yield therapeutic levels of drug in the intraocular fluids and clinical responses have been documented; however, relapse is common. The efficacy of cytostatics is dependent on intraocular pharmacokinetics, which are not well understood [58]. Presently, there is no evidence that intraocular lymphomas should be treated in a different way with respect to PCNSL without intraocular disease.

6.2. Chemotherapy as exclusive treatment

Chemotherapy as exclusive treatment for PCNSL is an interesting but still investigational strategy. Treatment-related neurotoxicity in PCNSL patients has not been clearly defined due to the small number of long-term survivors reported in the literature. The cumulative incidence varies from 5 to 10% at 1-year, and 25 to 35% at 5 years [45]. Age >60 years, post-radiotherapy chemotherapy and high-dose radiotherapy have been proposed as risk factors [8,26]. A direct relationship between age and severe neurotoxicity has been reported, with a 5-year risk of 48, 25 and 9% for patients aged 60, <60 and <40 years, respectively [59]. The appearance of late toxicity seems to reflect a predisposition to vascular injury at the site of the original lymphoma. In practice, half the patients develop a recurrence of their original symptoms without evidence of relapsed lymphoma. One-third of these patients died of complications related to the neurotoxicity [47]. Some authors have proposed to treat patients with chemotherapy alone, delaying radiotherapy at time of relapse in complete responders, as a major strategy to minimize neurotoxicity [55]. Since only a few prospective non-randomized trials assessing the impact on survival and toxicity of chemotherapy alone have been reported, the real efficacy of this strategy has not yet been defined. Furthermore these studies had a small sample size, included a few relapsed or histologically unproved cases, and had a short follow-up [55,60]. Primary chemotherapy consisted of a high-dose-methotrexate-containing regimen alone [50] or in combination [55,60], achieving a response rate of

85–100%, and a complete remission rate > 75%, but showing an extremely variable actuarial survival. In other small series, this strategy has produced response rates in excess of 90%, and patients who relapsed were effectively salvaged with additional chemotherapy or radiotherapy [61]. In published prospective trials, HD-MTX alone produced a 52–100% response rate and a 2-year survival of 61–63% [50,62–64], while results with HD-MTX-based polychemotherapy were 65–100% and 65–78%, respectively [65]. In a comparison of older patients treated with or without WBRT following HD-MTX-based chemotherapy [66], chemotherapy alone markedly reduced the risk of neurotoxicity, and although there was a higher relapse rate in patients treated without WBRT, there was no difference in survival (median 32 months) between these two subgroups. In a retrospective analysis of 378 patients, it was observed that WBRT did not improve survival in patients achieving complete remission after HD-MTX [23]. These data seem to indicate that it is feasible to treat PCNSL using chemotherapy alone. Given the extremely high risk of treatment-related neurotoxicity, chemotherapy alone should be considered in patients over the age of 60. Future studies, in larger series, should validate the chemotherapy alone strategy, as well as other strategies to dose intensify chemotherapy and eliminate the need for WBRT, perhaps in randomised trials.

6.3. Treatment of elderly patients

Radiation therapy is the conventional choice in elderly patients who cannot receive upfront chemotherapy. In these cases, WBRT using 40–45 Gy followed by a boost to the tumour-bed of 10 Gy was suggested as the optimum treatment [20]. Higher doses and larger radiation volumes or hyperfractionation increased treatment-related toxicity without any improvement in outcome. In elderly patients with a good performance status, chemotherapy alone is suitable for individual clinical use on a type R basis [61]. In a group of 13 elderly patients (median age, 74 years) treated with a variable chemotherapy regimen, including mostly high-dose methotrexate (1–3.5 g/m^2) alone or in combination with thiotepa, vincristine and cytarabine, a complete remission rate of 72% was achieved with a remarkable improvement in Karnofsky PS and cognitive functions. Six patients relapsed (5–20 months); four of them were irradiated as part of salvage therapy, achieving three complete responses. Six patients were alive with a median follow-up of 13 months. No cases of treatment-related neurotoxicity were observed in complete responders, but follow-up is too short to draw firm conclusions. Considering these findings and the relation between age, use of radiotherapy and severe neurotoxicity, chemotherapy alone appears an efficient and safe therapeutic alternative for elderly patients. A very preliminary experience showed that temozolomide could be active against PCNSL in elderly patients in whom HD-MTX-based chemotherapy is contraindicated.

6.4. Treatment of histologically unproved PCNSL

Occasionally, patients in whom radiological assessment has risen suspicion of PCNSL are not referred for histological assessment due to the frequent involvement of vital 'untouchable' structures, localized deeply into the brain, or to the presence of intracranial hypertension. Regression after steroid therapy, deep location of disease and neuroimaging appearance strongly support PCNSL diagnosis. However, only half of patients with "vanishing tumours", that is lesions regressing after steroids are actually PCNSL [67]. Confirmatory biopsy is thus mandatory. Treating a patient with unconfirmed PCNSL generates ethical and medical problems. In the past, these patients were referred for radiation therapy alone. This decision is still valid since there is a lack of randomized trials demonstrating the superiority of combined treatment compared with radiotherapy alone. However, large retrospective [20,45] and prospective [47] experiences suggest that the addition of chemotherapy significantly improves outcome, mainly in young patients with good PS. High-dose methotrexate-containing chemotherapy followed by radiation therapy is suitable for individual clinical use in histologically unproven PCNSL on a type 3 level of evidence for patients medically fit to undergo systemic chemotherapy.

6.5. Treatment of relapsed patients

The median survival of untreated patients with PCNSL after first-line treatment failure is 2 months. Salvage therapy achieves a further complete remission in many cases, with consequent symptomatic and survival improvement [26,43]. Median survival after relapse for patients responding to second-line treatment is 14 months, the time to relapse (cut-off: 12 months) being the main independent indicator of survival. There is no standard approach to patients with relapsed CNS lymphoma who have already received upfront systemic chemotherapy. Conclusions regarding the optimum second-line treatment cannot be made due to the extremely heterogeneous treatment modalities used in published series. In general, relapses in the brain or spinal cord after combined treatment necessitate further chemotherapy, which may or may not be followed by irradiation if this is still feasible. Salvage WBRT has been associated with an overall response rate of 60–74% and a median survival after relapse of 11–19 months in patients who experienced failure after initial HD-MTX [68,69]. Ocular recurrence can be treated with RT or with HD-araC which gives a survival lightly longer than that obtained with recurrences at other sites [26]. Meningeal relapse can be treated with spinal-cord irradiation or intrathecal chemotherapy. In some cases, re-irradiation of relapsed lesions has also been indicated. In patients relapsed after chemotherapy as exclusive first-line treatment, some authors have suggested that chemotherapy is used again as salvage strategy [55,70]. The most used cytostatic in patients who have relapsed after high-dose

methotrexate is cytarabine, but procarbazine, vincristine, cisplatin, temozolomide and several other drugs have also been used. Re-induction with HD-MTX resulted in a response in approximately 50% of patients with a median PFS of 10 months [71].

6.6. New active drugs and therapeutic options

High-dose chemotherapy with autologous peripheral blood stem cells transplantation (PBSCT) is an investigational therapeutic alternative (Table 1). The experience is still very limited, but attractive preliminary results were achieved in small pilot studies [72,73]. High-dose chemotherapy supported by APBSCT has been used as a strategy to dose intensify chemotherapy given to patients with newly diagnosed or relapsed PCNSL. Theoretically, this strategy can be used to replace WBRT in an effort to avoid treatment-related neurotoxicity. In patients with newly diagnosed PCNSL, there have been two small APBSCT phase II trials. In one study, 28 patients received five cycles of MTX 3.5 g/m^2 and two cycles of cytarabine 3 g/m^2 daily for 2 days, followed by BEAM (carmustine, etoposide, cytarabine and melphalan) consolidation chemotherapy in those patients with chemosensitive disease [74]. Fourteen patients completed the planned therapy and five remained in remission at a median of 26 months after transplant. Significant treatment-related toxicity was rare; however, only 50% of patients had chemosensitive disease and a significant proportion relapsed after transplant. In a recently reported multicenter trial of 30 patients with newly diagnosed PCNSL under the age of 65 [75], induction with a combination of MTX, thiotepa and cytarabine followed by high-dose chemotherapy with BCNU and thiotepa and hyperfractionated radiotherapy has been associated with 65% complete remission rate, and a 5-year OS of 87 and 69%, respectively for patients who received ASCT and for all enrolled patients. In a study on 22 patients with recurrent or refractory primary CNS or intraocular lymphoma, induction cytarabine and etoposide followed by high-dose chemotherapy with thiotepa, busulfan and cyclophosphamide produced a complete remission rate of 72%, with a 3-year overall survival of 64% [76]. However, there was a significant incidence of neurotoxicity as well as significant treatment-related morbidity/mortality in patients over the age of 60. The preliminary results from these trials using high-dose chemotherapy with APBSCT clearly indicate that this strategy is feasible in patients with PCNSL. It is possible that the patients treated at relapse who previously received WBRT will have a higher risk of neurotoxicity. As with conventional therapy, cytostatic drugs for induction and conditioning chemotherapy have been selected on the basis of their safety, efficacy against systemic lymphomas and ability to cross the BBB. The lack of cross-resistance with MTX has been an advantage when this strategy has been used as salvage therapy. The role of high-dose chemotherapy and APBSCT in PCNSL is still to be defined considering that worldwide experience is still limited, and further studies are needed to identify the optimal induction and high-dose chemotherapy regimens. The therapeutic benefit of graft-versus-lymphoma (GVL) effect after allogeneic PBSCT has been also reported in a case of PCNSL relapsed after high-dose methotrexate-containing chemotherapy and radiotherapy and after second-line conventional chemotherapy [77].

Reversible blood–brain barrier disruption (BBBD) by intra-arterial infusion of hypertonic mannitol followed by intra-arterial chemotherapy is a strategy that leads to increased drug concentrations in the lymphoma-infiltrated brain and may thus improve survival. In institutions with adequate expertise, upfront BBBD plus HD-MTX has been associated with acceptable morbidity, high tumour response and survival rates, and only a 14% loss of cognitive function at 1 year [78]. In relapsed patients, carboplatin based chemotherapy plus BBBD produced a 36% response rate, with a median duration of 7 months [79]. BBBD may prove most useful in the delivery of agents unlikely to traverse an intact BBB, such as unconjugated or radiolabeled monoclonal antibodies. However, this strategy is a procedurally intensive treatment, with vascular interventions, under general anaesthesia, monthly, over 1 year, and its role needs further investigations in PCNSL.

Temozolomide is an oral alkylating agent that spontaneously undergoes chemical conversion to MTIC (5-(3methyl-1-triazeno) imidaxole-4-carboxamide), resulting in 0-6 methylguanine-DNA methyltransferase depletion. This drug displayed excellent tolerability and a 26% response rate, mostly complete remissions, in a multicentre phase II trial on PCNSL relapsed or refractory to HD-MTX [80]. Considering that it permeates the BBB, it is well tolerated, even in elderly patients, and it exhibits additive cytotoxic activity with radiotherapy, temozolomide may be used as induction, maintenance or radiomimetic treatment against PCNSL. The latter application is supported by the positive experience in high-grade gliomas; however, the sole experience with radiomimetic in PCNSL patients (infusional 5 bromo-2′-deoxyuridine) has been associated with unacceptable neurotoxicity [81]. Preliminary data suggest that rituximab—temozolomide combination is well tolerated and active [82]. Rituximab, a chimeric monoclonal antibody directed against the B-cell specific antigen CD20, is an intriguing investigational drug. High doses of this drug can be safely infused to attain higher CSF concentrations. Anecdotal experience with intravenous rituximab showed disappointing results, while promising effects have been reported in a few cases of leptomeningeal lymphoma treated with intraventricular rituximab [83]. Duration of response, however, remains to be defined considering that treatment patients died early due to intraparenchymal progression. Topotecan, a camptothecin derivative that inhibits the enzyme topoisomerase I, produces an objective response in one-third of patients with refractory or relapsed PCNSL, with a 1-year PFS of 13% [84]. Some retrospective evidence suggests a positive impact

Table 1
Prospective phase II trials on high-dose chemotherapy supported by ASCT in PCNSL

Authors	Year	Therapy line	No. of pts	Induction regimen	Conditioning regimen	CRR (%)	Median f-up (months)	Survival data	Lethal toxicity (%)
Soussain et al. [76]	2001	2nd	22	araC-VP16	Thiotepa, CTX, busulfan	73	41	3-year EFS: 53%	23
Abrey et al. [74]	2003	1st	28	MTX-araC	BEAM	18	27	mEFS: 9 months	0
Stewart et al. [86]	2004	1st	11	MTX	Thiotepa, CTX, busulfan	82	22	3-year OS: 61%	18
Illerhaus et al. [75]	2006	1st	30	MTX	Thiotepa, araC, BCNU + RT	76	63	5-year OS: 69%	3
Colombat et al. [87]	2006	1st	25	MVBP	araC, ITX, BEAM + RT	64	25	3-year OS: 55%	6
Montemurro et al. [88]	2005	1st	23	MTX	Thiotepa, busulfan ± RT	81	15	mEFS: 17 months	13

CRR = complete remission rate; MTX = methotrexate; araC = cytarabine; CTX = cyclophosphamide; BEAM = carmustine, etoposide, cytarabine, and melphalan; RT = radiotherapy; MVBP = methotrexate 3 g/m^2/day, days 1, 5, VP16 100 mg/m^2 on day 2, BCNU 100 mg/m^2 on day 3, methylprednisolone 60 mg/m^2/day, days 1–5 and intrathecal prophylaxis. EFS = event-free survival; mEFS = median event-free survival; OS = overall survival.

of the addition of high-dose cytarabine to HD-MTX [23,85]. The latter observation constitutes the primary endpoint of one of the only two ongoing randomized trials in PCNSL.

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START METHODOLOGY

START is an evidence-based instrument. This means that statements on main clinical "options" are codified and accompanied by a codified "type of basis", as follows, according to a classification originally devised for the **START** project. The **START** Editorial team is glad to receive comments on this (please, address them to the START Secretariat). The background has been detailed in *Ann Oncol 1999; 10: 769-774.*

TYPE of OPTION

START provides the following diagnostic and treatment options. The "standard" and the "individualised" options are coupled with ranked types of basis,

- ***STANDARD ("standard", "recommended" [or "not recommended"])***
  This can be considered a conventional choice for the average patient.
- ***INDIVIDUALIZED ("suitable for individual clinical use")***
  This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.
- ***INVESTIGATIONAL ONLY ("investigational")***
  This is something which, in principle, can be offered to the patient only within a clinical study.

TYPE of BASIS for available options

START provides an appropriate basis for each clinical option. Types of basis are ranked in five levels.

- There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed
- ***"TYPE 1 evidence" (Randomised trial(s) available, strong evidence)***
  Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.
- ***"TYPE 2 evidence" (Randomised trial(s) available, weak evidence)***
  One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.
- ***"TYPE 3 evidence" (External controlled comparisons available)***
  Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.
- ***"TYPE R basis" (Rational inference)***
  Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).